

Message

From: Bussard, David [Bussard.David@epa.gov]
Sent: 6/5/2013 11:24:16 AM
To: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Chao Chen [ChaoChen25@comcast.net]
CC: Jinot, Jennifer [Jinot.Jennifer@epa.gov]
Subject: Fw: Kenny Crump thoughts on bottom up

I do think we can also question the Starr claim of greater certainty and using a high "N" by noting there is both considerable uncertainty and like small "N"s (sample points) in estimates of internal doses and relationships of external dose to changes in internal dose.

From: Bussard, David
Sent: Wednesday, June 05, 2013 7:21:14 AM
To: Chao Chen
Subject: Re: Kenny Crump thoughts on bottom up

I apologize for being unclear. By "average" I meant the slope between two points on the DR curve as versus the tangent slope at either point. (In physics of this were distance travelled v time it would be the "average" velocity as versus various instantaneous velocities. Sorry to be unclear.

D

From: chaochen25@comcast.net
Sent: Tuesday, June 04, 2013 10:13:55 PM
To: Bussard, David
Subject: Re: Kenny Crump thoughts on bottom up

David:

Rather than responding to your question today, I'd make a comment that is related to your last message which was very thoughtful. I do agree your overall thought direction as discussed and proposed. The first thing comes to my mind is what is the impact (over or under risk estimation) when BG1 and BG2 are "averaged" and a single cancer re incidence rate in the population is attributed to the "averaged" dose. Note the so-called "averaged dose" is not well defined here. Consider for instance an animal bioassay with the following design: 5 dose groups, d0, d1, d2, d3, and d5 with corresponding sample size (# of animals) 100, 80, 50, 20, and 10. In this case, the averaged dose for the study is $(100 \times d_0 + 80 \times d_1 + \dots + 10 \times d_4) / (100 + 80 + 50 + 20 + 10)$. We see that it is necessary to know the sample size for each dosed group before the averaged dose can be calculated, unless the number of animals in all groups identical. Anything short of these conditions would make the resultant "slope" calculated from the so-called "averaged dose" over or under estimate true risk. It is conceivable that one can construct examples by varying background dose distribution and risk response to come up with any results you want when the so-called "averaged" dose is used.

Chao

----- Original Message -----

From: "David Bussard" <Bussard.David@epa.gov>
To: "Chao Chen" <ChaoChen25@comcast.net>
Cc: "Jennifer Jinot" <Jinot.Jennifer@epa.gov>, "Ravi Subramaniam" <Subramaniam.Ravi@epa.gov>
Sent: Tuesday, June 4, 2013 8:56:06 AM
Subject: Re: Kenny Crump thoughts on bottom up

Chao,

On blackberry all I can see is actual text, so perhaps something else clarifies.

I am not understanding the idea that there is a relevant inflection point for formaldehyde.

For it to be relevant, I would think it would need to occur in the range relevant to env decisions (I.e. Lower than levels epa might try to control).

Can you explain why there might be an inflection (nondifferentiable) point in that dose range for formaldehyde? It seems like the bend in the apparent hockey stick would likely be above the decision range.

What am I missing?

David

From: chaochen25@comcast.net
Sent: Sunday, June 02, 2013 11:57:48 AM

To: Bussard, David
Cc: Jinot, Jennifer; Subramaniam, Ravi
Subject: Re: Kenny Crump thoughts on bottom up

David:

Please see the attached file that should help to illustrate my points. I can only send it as an attachment in order to preserve the math notations. I hope it is helpful.

Chao

----- Original Message -----

From: "David Bussard" <Bussard.David@epa.gov>
To: "Chao Chen" <ChaoChen25@comcast.net>, "Ravi Subramaniam" <Subramaniam.Ravi@epa.gov>
Cc: "Jennifer Jinot" <Jinot.Jennifer@epa.gov>
Sent: Saturday, June 1, 2013 6:12:40 PM
Subject: Re: Kenny Crump thoughts on bottom up

I think the B-Up approach could under-estimate slope at zero external dose anytime the dr curve has an increasing slope - not just when there is a hockey-stick. The hockey-stick is just a more pronounced case.

Kenny could have mentioned dose additive aty because it is one reason to assume a nonzero slope is likely at zero external dose.

I do think a very general critique would be the best starting point if it can be done. Especially if it could be done elegantly and clearly (like Kenny's early papers on why upperbound on slope was approx linear).

David

From: chaochen25@comcast.net
Sent: Thursday, May 30, 2013 9:36:35 PM
To: Subramaniam, Ravi
Cc: Jinot, Jennifer; Bussard, David
Subject: Re: Kenny Crump thoughts on bottom up

Ravi:

I missed the first day presentation because I could not get registered after I received your message.

While in principle I am inclined to agree with Kenny that a general paper is more appropriate when the bottom-up approach is at issue, but I am also concerned that Kenny may not be aware of the slippery nature of this issue, giving the fact that the issue is almost inseparable from formaldehyde data. The formaldehyde data suggest a hockey-stick dose-response relationship with a long pedal and short stick. This is important because such a dose-response function is not differential at the "bent point" at which a slope cannot be defined; if a slope is artificially derived using the left-hand side data then it will under estimate the slope in the right-hand side as David had pointed out before. I am not sure what Kenny had in mind when he mentioned "background additive". He seems to assume that a real dose-response function is always smooth (i.e., differentiable at all dose levels). This assumption is reasonable when there is only one background dose 0 but the issue could become slippery when someone begins to say that is not what he is talking about (I guess that you already have tasted something similar in Starr presentation). As a suggestion, if we want to write a paper criticizing the B-U approach, we may use a title such as "B-U approach is not well-defined under a hockey-stick dose-response function".

Chao

----- Original Message -----

From: "Ravi Subramaniam" <Subramaniam.Ravi@epa.gov>
To: "Jennifer Jinot" <Jinot.Jennifer@epa.gov>, "David Bussard" <Bussard.David@epa.gov>, chaochen25@comcast.net
Sent: Thursday, May 30, 2013 2:49:47 PM
Subject: Kenny Crump thoughts on bottom up

I had a chat with Kenny yesterday to get his opinion on the bottom up approach. He was totally in agreement with David's approach that the straight line cannot be an upper bound at zero endogenous dose and that it is not consistent with the additivity to background effects concept that gives rise to local linearity. He had read the paper and was thinking of the need to submit a paper of sorts to point this out. I mentioned to him we had drafted something that included multiple issues and a counter-example. However, he was very opposed to the idea of making this a formaldehyde paper. He would be interested in co-authoring with us only if it is a very general and simple paper that specifically speaks to additivity to background; does not want any of the kinetic issues related to the Starr modeling. I told him I would talk to the group and get back to him.

On a different note, at yesterday's ARA workshop Tom Starr totally misrepresented the counter-example we had worked up but there was no discussion time to call him out on what he showed as "EPA's work".

Ravi.